I. Markush Group Objections

The Examiner again rejects claims 57, 62-70, 73-81 and 94-100 as reciting improper Markush groups. *See* Paper No. 11, page 2, item 4. In their Amendment and Reply, filed December 5, 2000 (hereinafter "the December 5 Reply"), Applicants traversed the objection on the ground that: (1) all of the members of the Markush groups in the objected claims are closely related; and (2) a search of the subject matter of these claims would not place a "serious burden" on the Examiner.

The Examiner has maintained his objection because, in his view, "Applicant has failed to identify a common utility which is based upon a common structural feature disclosed as a basis for that common utility." Furthermore, the Examiner states that his objection is directed only to the form of the claims and does not relate to a restriction requirement. (The Examiner apparently interpreted Applicants' remarks in the December 5 Reply as a traversal of a restriction requirement). The Examiner states that he cited MPEP § 803.02, not in reference to a restriction requirement, but only because it "defines the proper content of a Markush Group."

From the Examiner's perspective, MPEP § 803.02 provides the test as to whether or not the content of a Markush group is proper; according to the Examiner, a Markush group is proper *only if* the elements of the group: (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. More subtly, the Examiner appears to be grafting a utility requirement onto the analysis of Markush groups. *This is not the appropriate test for determining whether a Markush group is proper.*

The criterion for determining whether or not a Markush group is proper was set forth by the CCPA in *In re Harnisch*, 631 F.2d 716 (CCPA 1980). There, the Court stated that

a Markush group is proper as long as there exists "unity of invention." *See Harnisch* at 721. *See also Ex parte Della Bella*, 7 USPQ2d 1669, 1669 (Bd. Pat. App. 1984). Unity of invention exists, according to the *Harnisch* Court, when the elements of a Markush group have "a community of properties justifying their grouping which [is] not repugnant to principles of scientific classification." *Harnisch* at 722. Consistent with this analysis, the MPEP broadly defines the proper content of a Markush group as follows: "The materials set forth in the Markush group ordinarily must belong to a recognized physical or chemical class or to an art-recognized class." MPEP § 2173.05(h).

The Examiner focuses his analysis on the concept of a "common functional utility," which he asserts must be shared by the elements of a Markush group. The *Harnisch* Court, however, did not state that the elements of a Markush group must possess a "common functional utility." Indeed, this phrase is found nowhere in the Court's opinion. The concept of a "common functional utility," upon which the Examiner bases his objection, is derived from *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. 1984). In referring to a "common functional utility," the Board in *Hozumi* was merely stating their interpretation of the *Harnisch* decision where the Court found that the Markush group at issue in that case possessed unity of invention.[1] *See Hozumi* at 1060. As stated by the *Hozumi* Board:

> [T]he claims in [*Harnisch*] were drawn to a class of compounds all of which were both disclosed and claimed as being "useful as dyestuffs." All of them were also both disclosed and claimed as being "coumarin compounds." Thus, *all of the claims had in common a functional utility related to a substantial, structural feature disclosed as being essential to that utility.*

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[1]As between a decision of the Board of Patent Appeals and Interferences and a decision of the CCPA, the CCPA's decision is controlling precedent.

Id. (Emphasis added). Nevertheless, the *Hozumi* Board acknowledged that the basic inquiry as to the propriety of a Markush group is "whether there existed 'unity of invention' or whether the claims were drawn to a collection of 'unrelated inventions'." *Id.* Thus, whether or not the elements of a Markush group possess a "common functional utility related to a substantial, structural feature disclosed as being essential to that utility," is merely one factor that can be used to support the basic underlying requirement of "unity of invention;" it is not the only way that unity of invention can be established.

Contrary to the Examiner's contention, MPEP § 803.02 itself *does not* require that members of a Markush group possess "a common utility which is based upon a common structural feature disclosed as a basis for that common utility." Rather, this section of the MPEP reads as follows: "*Broadly*, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." *Id.* (Emphasis added). This sentence -- especially considering the use of the word "broadly" -- indicates that these two criteria are *sufficient,* but not *necessary*, to establish unity of invention. Consistent with the *Hozumi* opinion, MPEP § 803.03 merely stands for the proposition that if members of a Markush group share a common utility and a substantial structural feature disclosed as being essential to that utility, that fact is only one element that may be used to demonstrate unity of invention. The principles established by the CCPA in *Harnisch* remain the true test for whether a Markush group is proper.

Returning to the actual, CCPA-promulgated test for determining whether a Markush group is proper; *i.e.*, whether the elements of the group possess unity of invention, it is clear that claims 57, 62-70, 73-81 and 94-100 indeed satisfy this test. First, as asserted in

Applicants' December 5 Reply, all of the members of the Markush groups in these claims are directed to nucleic acids that encode amino acid sequences shown in SEQ ID NOs: 2 and 4. Second, the nucleic acids of these claims encode the DR3-VI or DR3 polypeptides, or fragments thereof, and therefore "belong to a recognized genus of structurally related materials having a community of physical and chemical properties." *Della Bella* at 1669. The grouping of these nucleic acids would not be regarded as "repugnant to principles of scientific classification." *Harnisch* at 722. Finally, notwithstanding the Examiner's misplaced reliance on "common functional utility" as an element of the test for the propriety of a Markush group, Applicants assert that the members of the Markush group claims objected to by the Examiner indeed possess a common functional utility in accord with the analysis set forth in *Hozumi*. *Id.* at 1060. A discussion of the utility of Applicants' invention is presented immediately below.

Because claims 57, 62-70, 73-81 and 94-100 are proper Markush group claims under the controlling standard set forth in *Harnisch*, Applicants respectfully request that the Examiner's objection be reconsidered and withdrawn.

II. Rejections Under 35 U.S.C. § 101

The Examiner again rejects claims 27-119 under 35 U.S.C. § 101 as being drawn to an invention with no apparent or disclosed specific and substantial credible utility. *See* Paper No. 11, page 2, item 5. Applicants respectfully traverse the rejection.

The Examiner has the initial burden of challenging an Applicant's presumptively correct assertion of utility in the disclosure. *See In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). To meet that burden, the Examiner must provide evidence showing that one of

ordinary skill in the art would reasonably doubt the asserted utility. *See id.* Only after the Examiner has provided such evidence does the burden shift to the Applicant to provide rebuttal evidence "sufficient to convince [a person skilled in the art] of the invention's asserted utility." *Id.*

With respect to the instant application, the Examiner has not met his initial burden of demonstrating that a person skilled in the art would reasonably doubt Applicants' assertion that the polypeptides encoded by the claimed nucleic acids are useful in the treatment of diseases and disorders associated with abnormal apoptosis. As noted in the December 5 Reply, the specification clearly indicates that the receptors of the present invention induce apoptosis. For instance, in Example 6 of the specification it was shown that overexpression of the DR3 receptor mimics ligand activation and induces cell death.

The Examiner responds to this evidence of utility by stating that Applicants have "failed to identify the practical benefit to be derived from the disclosure of a protein which indices [sic: induces] apoptosis upon overexpression in a cell." Paper No. 11, page 3. Applicants respectfully disagree. In the December 5 Reply, Applicants argued that the polypeptides encoded by the claimed nucleic acids, by virtue of their ability to induce apoptosis, would be useful, *e.g.*, in the treatment of diseases associated with increased cell survival or insufficient apoptosis. Thus, Applicants have in fact identified a "practical benefit" that can be derived from polypeptides whose overexpression induces apoptosis.

The Examiner contends, however, that numerous receptor proteins induce apoptosis when activated by a ligand or overexpressed in a cell. Assuming this statement is true, it nonetheless has no bearing on the question of whether Applicants' claimed invention possesses legally-sufficient utility. The mere fact that many known biological molecules

possess a particular property does not mean that a newly discovered molecule that also possesses that property is not useful.

In short, the Examiner has failed to present evidence showing that a person of ordinary skill in the art would reasonably doubt Applicants' assertion of utility, and therefore has not met his initial burden.

The Federal Circuit has stated that, in the case of pharmaceutical inventions, even if the PTO has met its initial burden challenging an Applicant's assertion of utility, the Applicant's burden of rebuttal is nonetheless met by presenting evidence that the claimed compound possesses significant biological or therapeutic activity in a standard experimental model. *See Brana* at 1567 ("[A]pplicants provided ... test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor model *in vivo*. Such evidence alone should have been sufficient to satisfy applicants' burden.")

In the instant disclosure, Applicants have provided evidence that the ectopic expression of DR3 in standard cells lines (MCF7 breast carcinoma cells and 293 human embryonic kidney cells) induced rapid apoptosis. *See* Specification at page 69, lines 20-24. Therefore, even if the Examiner had met his initial burden in challenging Applicants' asserted utility, the experimental data in the instant disclosure would be sufficient to satisfy Applicants' burden of rebuttal.

The Examiner asserts, however, that "there is no evidence that the particular receptor identified in the instant application is in any way associated with the plurality of diseases and disorders listed on lines 23 to 26 on page 5 of the instant specification." Paper No. 11, page 3. The Examiner further asserts that simply because apoptosis is involved in the listed

diseases and disorders, it does not necessarily follow that the polypeptides encoded by Applicants' claimed nucleic acids have any role in those diseases or disorders. In other words, the Examiner, before accepting Applicants' assertion of utility, would require Applicants to show that DR3 plays a direct role in causing a particular disease associated with abnormal apoptosis.

As a preliminary matter, Applicants note that recent results suggest a link between DR3 and follicular lymphoma. *See* Warzocha *et al.*, BIOCHEM. BIOPHYS. RES. COMMUN. 242:376-379 (1998) (copy enclosed as Exhibit A). In this article, Warzocha and coworkers describe the isolation of an isoform of DR3 from mRNAs of a panel of human cell lines and tumor tissues obtained from patients with follicular non-Hodgkin's lymphoma. These results strongly suggest that DR3 functions to participate in lymphoid cell homeostasis. *See id.* at page 379 ("the 'programmed' change in DR3 alternative splicing may have functional effects not only in lymphocyte activation but also in lymphocyte differentiation and malignant transformation."). Thus, contrary to the Examiner's assertion, there does indeed exist evidence that the polypeptides encoded by the claimed nucleic acids of the present invention are associated with at least one of the diseases listed in the specification. The Warzocha data indicate not only that one of ordinary skill in the art would be convinced of Applicants' asserted utility, but these data also support Applicants' argument that the claimed invention possesses significant therapeutic activity, thus satisfying the utility requirement as articulated in *Brana*. *See id.* at 1567.

In the December 5 Reply, Applicants cite Example 10 of the *Revised Interim Utility Guidelines Training Materials* (hereinafter "the Training Materials") to support the utility

of the claimed invention. The Examiner, however, asserts that Example 12 of the Training Materials provides the more proper analysis of Applicants' claims.

Example 12 of the Training Materials demonstrates the application of the Utility Guidelines in the context of a hypothetical protein that has been isolated from a cell membrane and has been shown to bind to "protein X." In this example, the protein is characterized by the Applicant as "receptor A." The characterization of the protein as a receptor is based *solely on the fact that the protein was isolated from a cell membrane and that it binds to protein X.* Furthermore, the Applicant in this example asserts two utilities for the claimed invention. First, a method of identifying materials which bind to the receptor, and second, a method of making a monoclonal antibody.

According to the Training Materials, implicit in the asserted utilities is the use of compounds to exert control over the action of the receptor in the treatment of a disease or condition. The Training Materials conclude that, although the asserted utilities are *specific*, they are not *substantial*. The basis for this conclusion is that neither the Applicant nor the art of record disclosed any diseases or conditions associated with receptor A.

The fact pattern set forth in Example 12 of the Training Materials is distinguishable from the disclosure and claims of the present application. First, as compared to the hypothetical disclosure of Example 12 (where the only evidence to suggest that the identified protein was a receptor was the fact that it was isolated from a cell membrane), Applicants have provided substantially more evidence that the polypeptides encoded by the claimed nucleic acids are receptors and that they function in important physiological processes, namely apoptosis.

Second, in Example 12 there was no evidence provided that the receptor was associated with any disease or condition. In the present application, in contrast, Applicants have provided evidence that the polypeptides encoded by the claimed nucleic acids are integrally involved in the process of apoptosis.

Third, Applicants' disclosure indicates that the present invention is useful for the treatment of diseases associated with de-regulated or abnormal apoptosis. Therefore, unlike the disclosure described in Example 12, Applicants here have disclosed diseases and conditions associated with the claimed receptors and thus have defined a "real world context of use."

In summary, the fact pattern presented in Example 12 of the Training Materials is considerably different from the disclosure and circumstances surrounding the present application in terms of the utility requirement. Therefore, Applicants assert that the reasoning provided in Example 12 -- demonstrating why the utility requirement was not satisfied for the hypothetical protein described therein -- cannot be extended to the analysis of the utility of Applicants' claimed invention. As stated in the December 5 Reply, the more appropriate analysis would be under Example 10 of the Training Materials which militates against a rejection of Applicants' claims for lack of utility.

In fact, as disclosed in the specification, the subject receptor protein signals death to the cell via its intracellular death domain. Such death signaling activity is a specific process with a specific pathway that is certainly not a general property of all receptors. Moreover, the Examiner repeatedly refers to this receptor as an "orphan receptor," presumably because its ligand was not known at the time of filing. In essence, the Examiner is imposing a per se rule that a protein that happens to be a receptor cannot be patented until a natural ligand

is identified. This rule regarding the utility of a receptor has absolutely no basis in law, nor does it make sense scientifically. Applicants have disclosed the activity and function of the receptor irrespective of the identity of its naturally occurring ligand(s). It is commonly known in the art, and disclosed in detail in the instant specification, that a receptor's activity can be activated or blocked by an agonist or antagonist without any knowledge whatsoever of its ligand. Indeed, Applicants have provided such agonists and antagonists in the instant specification, including, for example, antibodies and antibody fragments that bind to the receptor. Thus, Applicants have described and enabled the DR3 protein by its specific function, as well a methods of effecting or blocking this specific function using molecules that bind to the protein. The utility requirement of 35 U.S.C. § 101 has been satisfied and is in no way even implicated by its supposed status as an "orphan receptor."

Applicants reiterate that the invention claimed in the instant application possesses a specific, substantial, and credible utility. The Examiner has not met his burden of showing that one skilled in the art would reasonably question Applicants' assertion of utility. Even if the initial burden has been met, Applicants have satisfied their burden of rebuttal by demonstrating, *e.g.*, in Example 6 of the disclosure, that the claimed invention possesses significant biological activity in a standard experimental model. *See Brana* at 1567. The Warzocha results, discussed above, provide even more support for Applicants' assertion of utility under the analytical framework set forth in *Brana*. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 101 for lack of utility be reconsidered and withdrawn.

III. Rejections Under 35 U.S.C. § 112, First Paragraph

A. Utility

The Examiner again rejects claims 27-119 under 35 U.S.C. § 112, first paragraph, for failing to adequately teach how to use the instant invention. The rationale for this rejection is the same as that which the Examiner provides to support his rejection under 35 U.S.C. § 101. *See* Paper No. 11, page 4, item 6. Applicants respectfully traverse the rejection and note that this rejection has been addressed above with regard to the rejection of these claims under 35 U.S.C. § 101. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. Enablement

The Examiner again rejects claims 43-56 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and use the invention. *See* Paper No. 11, page 4, item 7. The Examiner states that the claims expressly require the biological material recited therein to make and use the claimed invention.

Applicants assert that a Declaration for Deposited Materials was submitted with the December 5 Reply. The Examiner asserts, however, "no such declaration is currently present in the instant application."

Applicants enclose herewith a copy of the Declaration for Deposited Biological Materials that was submitted originally with the December 5 Reply. In addition, Applicants enclose a photocopy of the date-stamped postcard acknowledging receipt of the Declaration by the USPTO on December 5, 2000, *i.e.*, before the Final Office Action (*see* Exhibit B). In view of the fact that a Declaration for Deposited Biological Materials has been properly

submitted, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 43-56 under 35 U.S.C. § 112, first paragraph.

IV. Rejections Under 35 U.S.C. § 102(b)

The Examiner maintains his rejection of claims 27-119 under 35 U.S.C. § 102(b) as being anticipated by Kitson *et al.*, NATURE 384: 372-375 (Nov. 1996). *See* Paper No. 11, page 4, item 8. According to the Examiner, "because of the rejection of these claims for lack of utility under the first paragraph of 35 U.S.C. § 112 above, the instant application does not receive the benefit under 35 U.S.C. § 120 from any prior applications." Applicants respectfully traverse the rejection.

Applicants reiterate that the utility requirement of 35 U.S.C. §§ 101 and 112, first paragraph, are completely satisfied for the reasons discussed above and in the December 5 Reply. Accordingly, the invention is disclosed in Applicants' earlier-filed applications in the manner required by 35 U.S.C. § 112, first paragraph. Therefore, for the reasons set forth in the December 5 Reply, Kitson *et al.* is not prior art under 35 U.S.C. § 102. In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-119 under 35 U.S.C. § 102(b).

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be

withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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